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Cardiac involvement in tuberous sclerosis

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Abstract

***Objective*—To assess the incidence, importance, and history of cardiac involvement in infants and children with tuberous sclerosis.**

***Design*—Prospective study; clinical examination, sector and Doppler echocardiography, standard and ambulatory electrocardiography.**

***Setting*—A tertiary referral centre.**

***Patients*—21 patients with tuberous sclerosis aged 1 day to 16 years (mean 6·3 years); follow up investigations were available in 14 cases (10 retrospective, 4 prospective; mean follow up 4·3 years).**

***Results*—Multiple cardiac rhabdomyomas in the right ventricle (11) and left ventricle (14) as well as in the right atrium (1) were present in 14/21 patients. Two of them had obstruction of the left ventricular inflow and outflow tract related to a tumour. In the remaining 7 patients, echocardiography was normal in 4 and equivocal in 3 cases. The standard electrocardiogram (n = 20) showed ventricular hypertrophy (2), ventricular pre-excitation (1), arrhythmias (2), and repolarisation disturbances (4) in 7/13 patients with rhabdomyomas but was normal in all patients with a normal or equivocal echocardiogram. The ambulatory electrocardiogram (n = 19) showed frequent premature atrial (2) and polymorphous ventricular (2) contractions. The polymorphous ventricular contractions coexisted with rhabdomyomas. No arrhythmias that needed medical treatment were found. Follow up investigations showed return to a normal standard electrocardiogram in 3 patients. Definite regression or complete disappearance of the tumour occurred in 6 infants.**

***Conclusions*—Cardiac rhabdomyomas, although often present in these patients with tuberous sclerosis, caused neither major arrhythmias nor haemodynamic obstruction except in the neonatal period. The indication for operation is limited to cases with life threatening obstruction or arrhythmias refractory to medical treatment.**

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Tuberous sclerosis is one of the neurocutaneous syndromes with autosomal dominant inheritance and has a reported incidence of 1:10 000. Mental retardation, cerebral convulsions, and adenoma sebaceum are the characteristic signs of the disease and were described in 1908 by Vogt.[1] Besides the neurocutaneous abnormalities many other organ systems may be involved.[2–4] Primary and secondary criteria for the diagnosis of tuberous sclerosis were defined by Gomez.[5]

In 1862 von Recklinghausen first described the coincidence of cardiac tumours and intracerebral sclerotic areas in a newborn baby.[6] Recent echocardiographic studies reported a 50%–64% incidence of cardiac rhabdomyomas detected by ultrasound in patients with tuberous sclerosis.[7–9]

Our prospective study was performed to examine the occurrence and the haemodynamic or arrhythmic relevance of cardiac rhabdomyomas in infants and children with tuberous sclerosis.

Patients and methods

PATIENTS

Twenty one patients, 15 male and six female aged 1 day to 16 years (mean 6·3 years), were studied. The diagnosis of tuberous sclerosis was based on the criteria described by Gomez,[5] every patient had typical white spots and characteristic subependymal hamartomas in the cranial computed tomogram. All patients had a history of cerebral convulsions. At the time of the study, three patients who were not on medication had no seizures. The remaining 18 patients were treated with anticonvulsive drugs, nine of them successfully.

The age at the time of diagnosis varied between 1 day and 8 years (mean 1·7 years). The most frequent condition leading to the diagnosis of tuberous sclerosis was cerebral convulsions (14 patients). In two patients, a known family history caused the patients to be examined. Five patients presented first with cardiac symptoms leading to the diagnosis of tuberous sclerosis: a heart murmur was the indication for an echocardiographic examination in four infants. In the other patient, the diagnosis of rhabdomyomatosis was already known before birth due to fetal arrhythmias and consecutive echocardiographic examinations.

Follow up investigations were available in 14 cases, including 10 with retrospective studies (follow up 0·5–8·3 (mean 5·3) years) and four neonates with prospective control examinations (follow up 0·6–3·5 (mean 1·9) years).

METHODS

Besides a physical examination, the investigative programme included a complete echocardiographic study and a standard and a 24 hour ambulatory electrocardiogram.

The echocardiographic studies, documented on video tape, were assessed by two

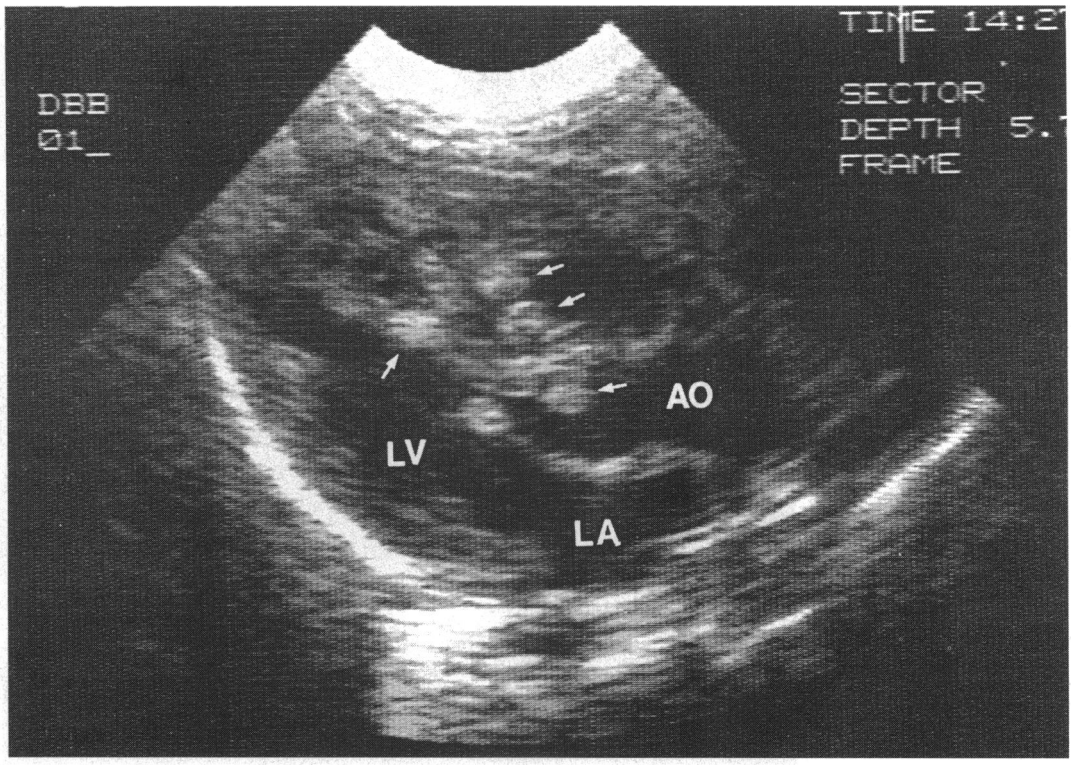

Figure 1 Multiple intramural and intracavitary rhabdomyomas in a 4 week old baby with tuberous sclerosis. LV, left ventricle; LA, left atrium; Ao, ascending aorta; arrows, rhabdomyomas.

independent observers. High resolution sector echocardiographic images were obtained by 3·5, 5·0, or 7·5 MHz transducers with a mechanical sector scanner from the parasternal, apical, and subcostal position. Rhabdomyomas were diagnosed if discrete areas of increased acoustic density were visible within a cardiac cavity or wall in at least two imaging planes. In cases where only very small echogenic regions were noticed within the interventricular septum or the right or the left ventricular free wall, the patient was classified as equivocal. Doppler studies were performed to exclude obstructions related to a tumour.

Twelve lead standard electrocardiograms were available in all but one patient, who had echocardiographic evidence of rhabdomyomas.

Ambulatory electrocardiographic studies were performed with a continuous recording system (Oxford Medilog 4500). Interpretation of the data were based on automated reports with manual interaction during processing and a careful review of the complete 24 hour electrocardiogram plotted on paper. Ambulatory electrocardiograms were lacking in one patient with and in another one without echocardiographic evidence of heart tumours.

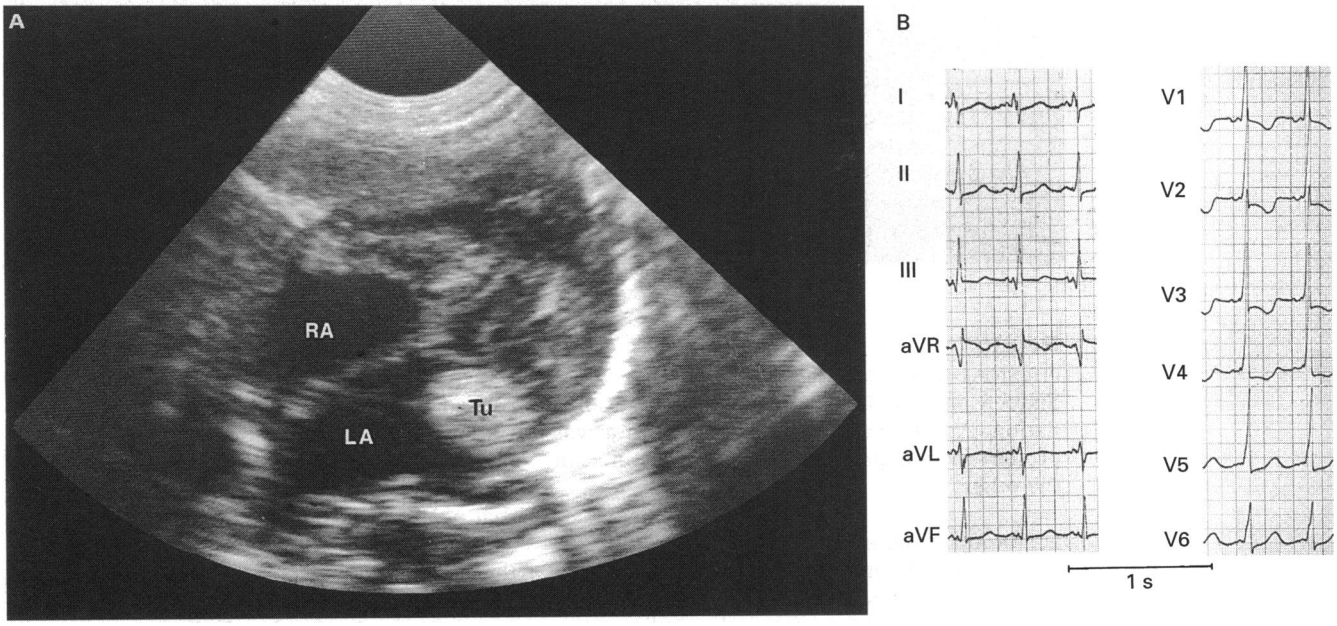

Figure 2(A) Echocardiogram of a 5 week old baby (subcostal view). A large tumour is adjacent to the mitral valve and obstructs the inflow tract. LA, left atrium; RA, right atrium; Tu, tumour. (B) Electrocardiogram of the same patient shows ventricular pre-excitation with negative delta waves in leads III and avF, and R > S in lead V_1 consistent with a left posterior accessory pathway.

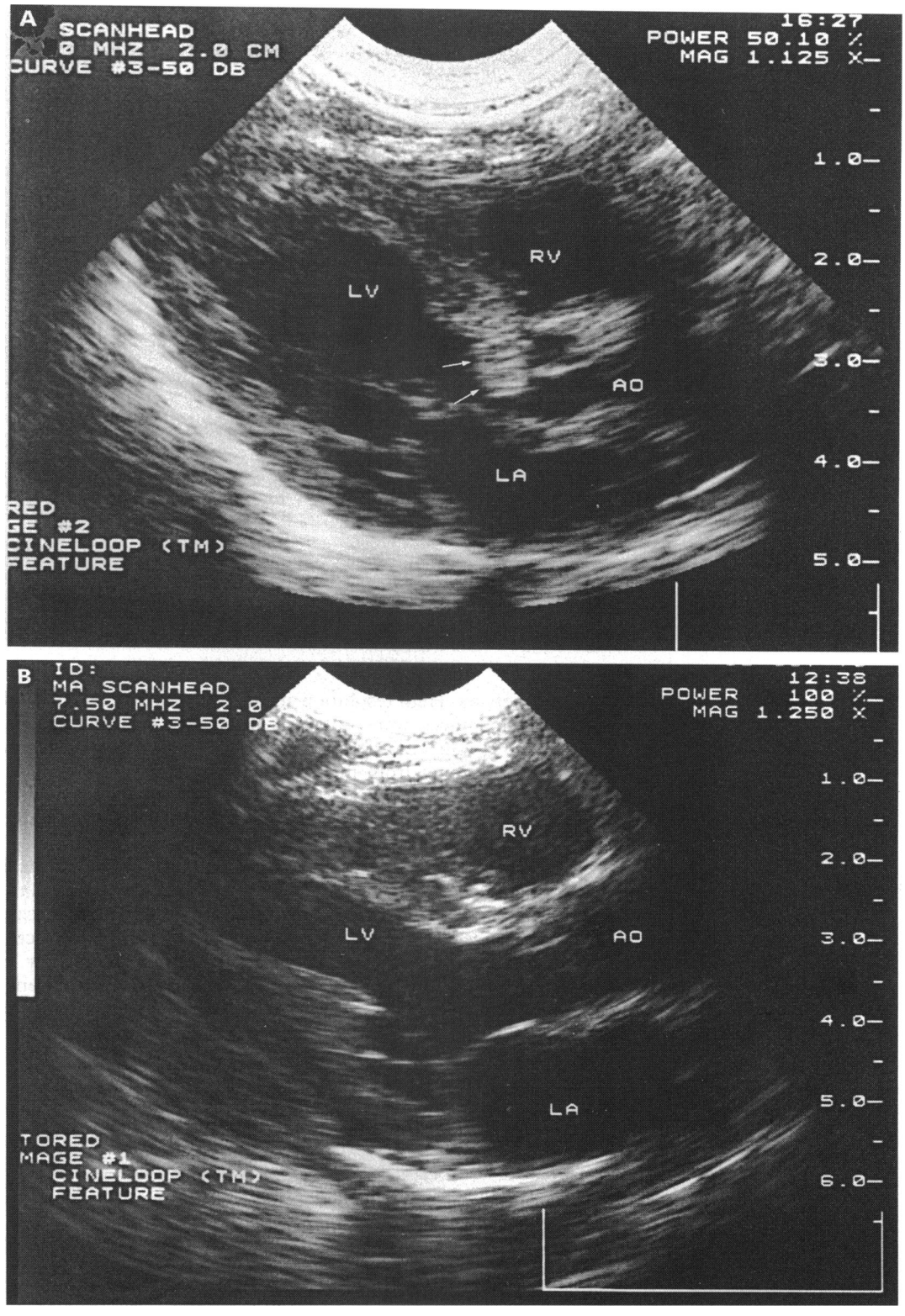

Figure 3(A) Six week old baby with tuberous sclerosis. Echocardiography shows an echogenic tumour arising from the interventricular septum with obstruction of the left ventricular outflow tract (Doppler gradient 33 mm Hg). (B) Echocardiogram of the same patient two years later: tumour is almost completely regressed except for small echogenic areas in the subaortal portion of the interventricular septum. LV, left ventricle; RV, right ventricle; LA, left atrium; Ao, ascending aorta; arrow, tumour.

Results

PHYSICAL EXAMINATION

Sixteen patients had a normal cardiac examination. An organic systolic heart murmur was present in four patients and an arrhythmia in the other.

ECHOCARDIOGRAPHIC STUDIES

The echocardiographic examination was normal in four and equivocal in three patients. In the remaining 14 cases echocardiography showed multiple rhabdomyomas in the right ventricle (11) and left ventricle (14) (fig 1) as well as in the right atrium (one). Two patients, both neonates, had obstructions related to a tumour. In the first case, a large tumour adjacent to the mitral valve led to obstruction of the left ventricular inflow (fig 2). Recurrent episodes of pulmonary oedema that needed assisted ventilation were the indication for surgical resection of the tumour at the age of five weeks. The outcome was unfavourable and the infant died from progressive mitral valve insufficiency one month after the operation. In the second case, Doppler echocardiography confirmed that a

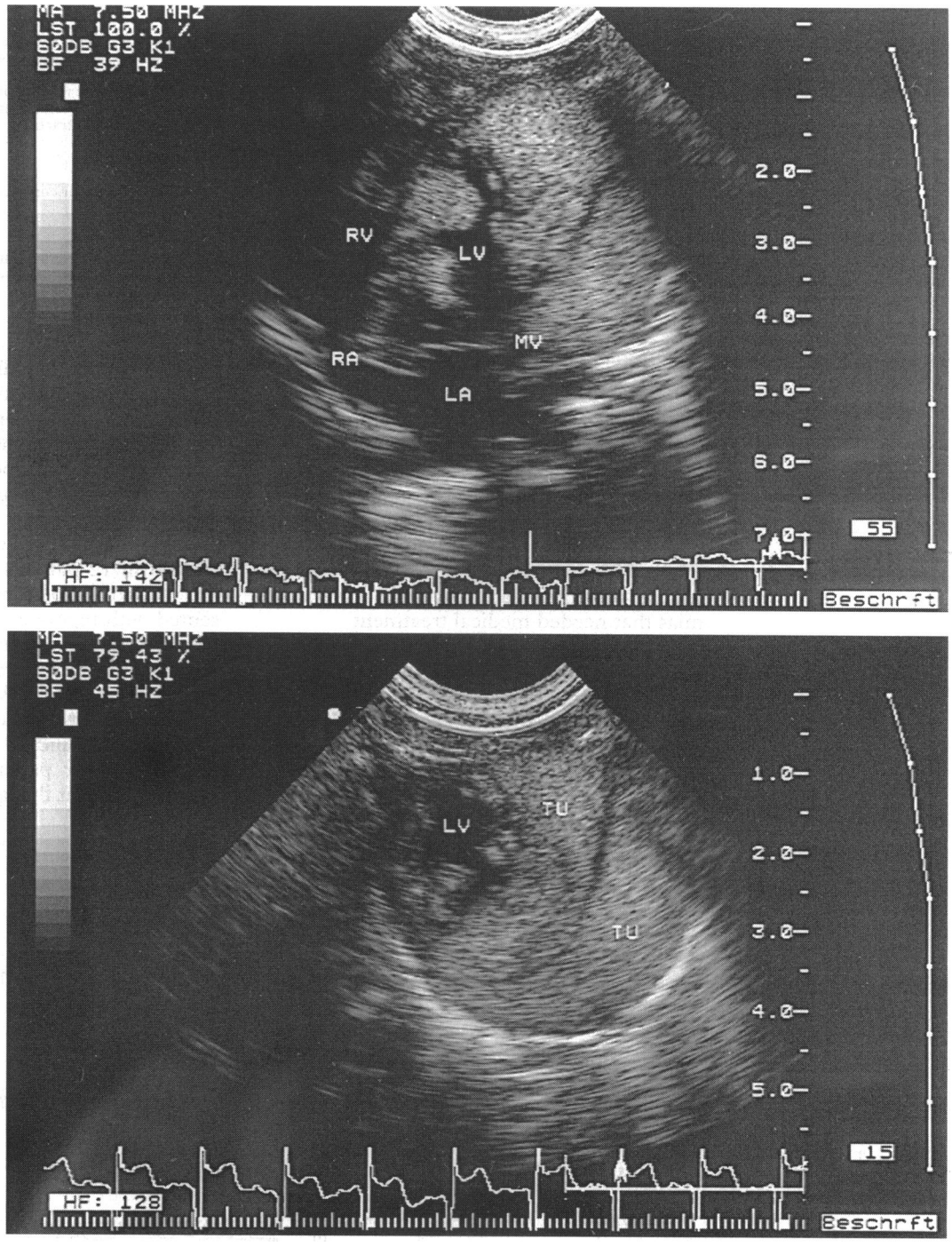

Figure 4 Apical four chamber view (above) and parasternal short axis view (below) in a 3 day old baby shows multiple rhabdomyomas at the intraventricular septum and a very large tumour on the lateral and apical aspect of the left ventricle. Regression of tumour was obvious seven months later. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; Tu, tumour; MV, mitral valve.

tumour that arose from the subaortic intraventricular septum caused an obstruction to the left ventricular outflow tract (fig 3A). The patient was asymptomatic and therefore surgery was not considered necessary. Follow up investigations showed spontaneous regression of the tumour within two years (fig 3B).

Besides these two infants with obstructive lesions, haemodynamic relevance could be excluded by Doppler sonography in two further neonates: one with a large tumour within the right ventricle close to the tricuspid valve, the other with an extended tumour on the lateral and apical aspect of the left ventricle (fig 4).

STANDARD ELECTROCARDIOGRAM

Standard electrocardiograms were available in 20 patients (table 1). Pre-excitation without episodes of supraventricular tachycardia was found in the patient with a large tumour adjacent to the mitral valve (fig 2). The standard electrocardiogram was normal in all patients with normal or equivocal echocardiographic investigation, but the electrocardiogram was abnormal in seven of 13 patients with echocardiographic evidence of rhabdomyomas.

24 HOUR AMBULATORY ELECTROCARDIOGRAM

Table 2 shows the results of the 24 hour ambulatory electrocardiographic studies, available in 19 patients. There was a predominant sinus rhythm in all patients. Occasional junctional escape rhythms and a few short episodes of second degree atrioventricular

Table 1 Standard electrocardiogram in 20 patients with tuberous sclerosis

Result	*No*
Normal	13
Abnormal:	6
Ventricular pre-excitation	1
Premature atrial contractions	1
Premature ventricular contractions	1
Ventricular hypertrophy	2
Repolarisation disturbances	4

Table 2 24 h Ambulatory electrocardiogram in 19 patients with tuberous sclerosis

Sinus rhythm	19
Junctional escape rhythm (intermittent)	1
Second degree AV block (intermittent)	1
Premature atrial contractions:	
Frequent	2
Blocked	1
Consecutive	1
Premature ventricular contractions:	
None	7
<100/24 h	10
Frequent	2
Supraventricular or ventricular tachycardia	0

AV, Atrioventricular.

block occurred each in one patient. Two of six patients without confirmed cardiac tumours had a few (<100/24 hours) premature ventricular contractions but 10 of 13 patients with heart tumours had at least a few premature ventricular contractions. Frequent premature atrial contractions were found in one patient with and one without rhabdomyomas. None of the 19 patients had episodes of supraventricular or ventricular tachycardia, or arrhythmias that needed medical treatment.

FOLLOW UP INVESTIGATIONS

Repeated echocardiographic studies were available in 14 patients. Ten children had 22 previous echocardiographic studies and four infants 21 prospective follow up studies (table 3). Definite spontaneous regression of a tumour or complete disappearance was found in six patients (Nos 1–6) with first investigation in infancy, whereas four patients (No 7–11) showed no change in their tumours during childhood. Spontaneous relief of the obstruction was documented in one infant (fig 3).

Repeated standard electrocardiograms were present in 12 patients with a total number of 45 electrocardiograms. Four patients presented with repolarisation disturbances at the first investigation, in two of them the electrocardiogram became normal before the last investigation (fig 5). Arrhythmias disappeared in three of five patients during follow up. Overall, the standard electrocardiogram was normal in four patients at the first and in seven patients at the last investigation.

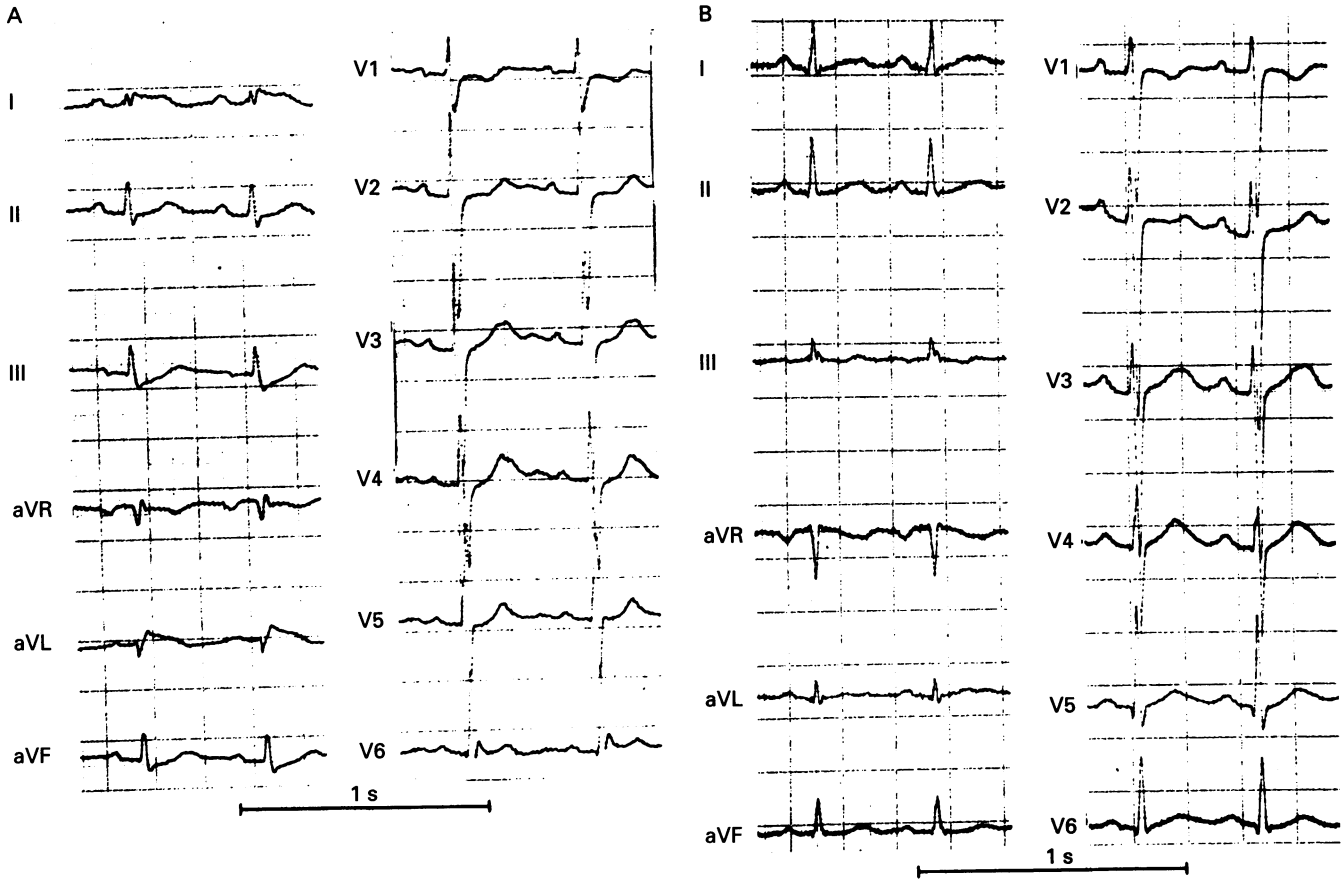

Figure 5(A) Electrocardiogram of a 23 month old boy with an echogenic tumour in the apex of the left ventricle shows repolarisation disturbances including ST segment elevation in lead I and avL. (B) Electrocardiogram of the same patient 3·5 years later: completely normal.

Table 3 Echocardiographic findings in 14 patients with follow up

Patient No	First study		Actual study		Follow up (mo.)
	Age	Tumour	Tumour	Development	
1	intrauterine	+	+	Regression	22*
2	6 days	+	+	Regression	42*
3	3 days	+	+	Regression	7*
4	1 month	+	+	Regression	23*
5	4 months	+	+	Regression	78
6	6 months	+	+	Regression	82
7	46 months	+	+	No change	73
8	59 months	+	+	No change	82
9	103 months	+	+	No change	73
10	123 months	+	+	No change	71
11	68 months	?	?		5
12	3 months	?	—		29
13	44 months	—	?		100
14	25 months	—	—		48

*Prospective follow up; ?, equivocal.

Discussion

The incidence of rhabdomyomas in patients with tuberous sclerosis had been underestimated until sector echocardiography allowed non-invasive detection of tumours by screening.[10] Image quality with high frequency transducers is usually good enough in infants and children to detect even small intramural tumours. Magnetic resonance imaging has proved to be of additional value especially in older patients and in patients with poor image quality due to bone and lung interference.[11 12]

Sixty five per cent of our patients with tuberous sclerosis had echocardiographic evidence of rhabdomyomas which corresponds to a reported incidence of 50%–64% in previous studies.[7–9] There is a wide range of symptoms of tumours from total absence of symptoms to intrauterine or sudden postpartum death.[13 14] Fetal hydrops, intrauterine arrhythmia, or multiple tumours detected by fetal ultrasound screening may be the first symptoms that lead to the diagnosis of tuberous sclerosis before delivery.[15–17] Furthermore, tuberous sclerosis has been diagnosed by ultrasound screening already in early fetal life in patients with a known family history of the disease.[18 19] In our study, cardiac manifestation led to the diagnosis in five patients whereas nine patients with rhabdomyomas were completely asymptomatic and the tumours were only detected by screening of patients with tuberous sclerosis.

Syncopes in patients with tuberous sclerosis are likely to be attributed to cerebral causes: over 90% of children with tuberous sclerosis have epilepsy.[20] Nevertheless, cardiac involvement includes the possibility of syncopes due to severe arrhythmias or embolisation of tumours. Until now, there is little information on the incidence and importance of arrhythmias in infants and children with tuberous sclerosis. To our knowledge, there are only two previous reports that prospectively looked for arrhythmias in 11 and seven patients with tuberous sclerosis[8 21]: in summary, two of the 18 patients showed important arrhythmias in the ambulatory electrocardiogram—that is, supraventricular tachycardia. One of them had rhabdomyomas. Our study gives further support to the assumption that an arrhythmic origin of syncope is unlikely. The ambulatory electrocardiogram disclosed no important arrhythmias in patients with or without rhabdomyomas, although ventricular extrasystoles occurred more often with rhabdomyomas. A large tumour adjacent to the mitral valve was the underlying cause of ventricular pre-excitation in one patient, but acute deterioration was related to obstruction of the left ventricular inflow tract and not to supraventricular tachycardia.

Apart from arrhythmias, cerebral embolisation is considered to be a potential cause of syncopes.[22] None of our patients with intracavitary rhabdomyomas showed a pedunculated origin or an extended tumour mobility likely to cause embolisation. Although a higher incidence of strokes has been reported in patients with tuberous sclerosis, there is no confirmation that cerebral embolisation by fragments of cardiac rhabdomyomas plays a part.[23]

Spontaneous regression and even complete disappearance of rhabdomyomas has become apparent since serial echocardiographic studies are available.[10 24 25] Our study confirms these findings; all four infants prospectively followed up showed spontaneous regression of their tumours. This became even more apparent when compared with the growing heart chambers. Obstruction related to tumours was found only in early infancy.

The indication for surgical treatment of cardiac rhabdomyomas have changed during the past years. Recommendations of radical excision of the tumour in symptomatic or even asymptomatic patients are now obsolete.[26 27] The benign natural history restricts the indication for an operation to patients with life threatening obstruction or arrhythmias refractory to medical treatment.

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CORRECTION

Comparative ability of dobutamine and exercise stress in inducing myocardial ischaemia in active patients. *T H Marwick, A M D'Hondt, G H Mairesse, T Baudhuin, W Wijns, J M Detry, J A Melin.*
The authors of this article miscalculated some percentages in tables 2 and 6 (*Br Heart J* 1994;72:31–8). Their corrected versions of these tables appear alongside.

Table 2 Electrocardiographic responses during maximal (P value) and submaximal exercise and dobutamine stress testing

	All patients	*Maximal*	*Submaximal*	*Maximal vs submaximal*
		Exercise		
Sensitivity	43/56 (77%)	39/44 (89%)	4/12 (33%)	0·0003
Specificity	13/30 (43%)	4/19 (21%)	9/11 (82%)	0·002
Accuracy	56/86 (65%)	43/63 (68%)	13/23 (57%)	NS
		Dobutamine		
Sensitivity	18/56 (32%)	13/22 (59%)	5/34 (15%)	<0·001
Specificity	19/30 (63%)	7/13 (54%)	12/17 (71%)	NS
Accuracy	37/86 (43%)	20/35 (57%)	17/51 (33%)	0·02

Table 6 Perfusion abnormalities on scintigraphy during maximal and submaximal exercise and dobutamine stress testing

	All patients	*Maximal*	*Submaximal*	*Maximal vs submaximal*
		Exercise		
Sensitivity				
Overall	41/56 (73%)	33/44 (75%)	8/12 (67%)	NS
Single vessel disease	14/22 (64%)	12/18 (67%)	2/4 (50%)	NS
Multivessel disease	27/34 (79%)	21/26 (81%)	6/8 (75%)	NS
Specificity	21/30 (70%)	13/19 (68%)	8/11 (73%)	NS
Accuracy	62/86 (72%)	46/63 (73%)	16/23 (70%)	NS
		Dobutamine		
Sensitivity				
Overall	35/54 (65%)	16/21 (76%)	19/33 (58%)	NS
Single vessel disease	15/22 (68%)	8/10 (80%)	7/12 (58%)	NS
Multivessel disease	20/32 (63%)	8/11 (73%)	12/21 (57%)	NS
Specificity	19/28 (68%)	7/11 (64%)	12/17 (71%)	NS
Accuracy	54/82 (66%)	23/32 (72%)	31/50 (62%)	NS